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JACC REVIEW TOPIC OF THE WEEK

Ancestry, Lipoprotein(a), and Cardiovascular Risk Thresholds

JACC Review Topic of the Week

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ABSTRACT

This study reviews ancestral differences in the genetics of the *LPA* gene, risk categories of elevated lipoprotein(a) [Lp(a)] as defined by guidelines, ancestry-specific Lp(a) risk, absolute and proportional risk, predictive value of risk thresholds among different ancestries, and differences between laboratory vs clinical accuracy in Lp(a) assays. For clinical decision-making, the preponderance of evidence suggests that the predictive value of Lp(a) does not vary sufficiently to mandate the use of ancestry-specific risk thresholds. This paper interprets the literature on Lp(a) and ancestral risk to support: 1) clinicians on understanding cardiovascular disease risk in different ancestral groups; 2) trialists for the design of clinical trials to ensure adequate ancestral diversity to support broad conclusions of drug effects; 3) regulators in the evaluation of the design and interpretation of results of Lp(a)-lowering trials with different Lp(a) inclusion thresholds; and 4) clinical laboratories to measure Lp(a) by assays that discriminate risk thresholds appropriately. (J Am Coll Cardiol 2022;80:934–946) © 2022 by the American College of Cardiology Foundation.

With a rapidly accumulating evidence base over the last decade, lipoprotein(a) [Lp(a)] is now generally accepted as a genetic, independent risk factor for cardiovascular disease (CVD) and aortic stenosis.[1,2] This is reflected by at least 7 national and international societies recommending the measurement of Lp(a) levels in either all adults at least once or in subjects in intermediate- or high-risk categories based on clinical characteristics. The development of new therapeutic modalities to inhibit translation of *LPA* messenger RNA in the hepatocyte[3] has allowed the testing of the "Lp(a) hypothesis," namely that lowering Lp(a) levels will lead to a reduction in CVD events. A major unresolved issue in the field is the appropriate interpretation of current data of risk thresholds according to ancestry. The relevance of this issue is reflected by the clinically significant differences in population mean Lp(a) levels.[4] Elevated Lp(a) may influence absolute risk across populations with differences in population mean Lp(a) levels and also influence proportional risk at the individual level irrespective of the population mean prevalence.

This review summarizes and interprets the literature on ancestral differences in Lp(a) levels, their measurement with current techniques, and their potential impact in the emerging field of Lp(a) in clinical trials, regulatory implications, clinical investigation, and clinical care.[5]

GENETIC ARCHITECTURE OF THE *PLG* AND *LPA* GENES

The plasminogen (*PLG*) gene is present in all mammals. The *LPA* gene coding apolipoprotein(a) (apo[a]) is located adjacent to *PLG* on the long arm of

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HIGHLIGHTS

- There is a 2- to 4-fold median difference in plasma Lp(a) levels among ancestral groups.
- The predictive value of Lp(a) levels does not generally vary enough across ancestral groups to require use of different ancestry-specific risk thresholds.
- In the design of studies evaluating strategies for management of patients with elevated Lp(a) levels, it is important to ensure adequate ancestral diversity to support broad conclusions about treatment effects.

chromosome 6 and is a more recent evolutionary arrival,[6] being present only in humans, the four Great Apes, Old World monkeys, and the hedgehog. The *LPA* gene evolved through duplication and remodeling of segments of the *PLG* gene and has no identified physiological function. The *LPA* gene is thought to have "convergently" evolved several times, once by duplicating 31 copies of kringle III (KIII) of *PLG* in the African and European hedgehog, then by duplicating KIV of *PLG* in Old World monkeys, and then again by duplicating both KIV and KV in apes and humans. As a result of remodeling during evolution, the *LPA* gene accumulated 10 subtypes of KIV of *PLG,* with 75% to 85% amino acid homology of the various *LPA* kringles with KIV of *PLG*. In addition, unlike the other KIV repeats, the KIV_2 subtype DNA was duplicated from 1 to >40 copies and has synonymous variations at the DNA level, but the protein sequences are identical. Furthermore, the protease-like domain of *LPA* lost the fibrinolytic activity of *PLG* due to a serine/isoleucine substitution for arginine/valine that prevents tissue plasminogen activators to convert apo(a) to a plasmin-like molecule.

Plasminogen binds both fibrin and oxidized phospholipids.[7] In contrast, as *LPA* evolved, it lost the ability of *PLG* to bind to fibrin and accumulate oxidized phospholipids through variations in the lysine-binding site of KIV_{10} in non-human primates and monkeys.[8] Interestingly, for unknown reasons, Lp(a) in humans has regained both the ability to bind fibrin and to preferentially accumulate oxidized phospholipids.[9,10] These regained properties may be one mechanism for the propensity of Lp(a) to mediate atherothrombosis and be identified an independent risk factor for CVD (**Figure 1**).

DIFFERENCES IN POPULATION MEAN Lp(a) LEVELS

The prevalence of elevated Lp(a) varies by geography. Using the updated 2022 global and continental population statistics, it is estimated that the prevalence of elevated Lp(a) (≥100-125 nmol/L, ~50 mg/dL), representing ~20% of the population, has increased from 1.4 billion to 1.5 billion relative to 2018[4] (**Figure 2**). Lp(a) is primarily genetically determined, with relatively small effects induced by diet, environment, hormonal status, and subclinical/clinical inflammation. In addition, natural variability in Lp(a) levels along a pre-set genetically determined baseline can occasionally occur in otherwise healthy, asymptomatic subjects, as documented when measured serially using rigorous methodology.[11] This natural variability is relevant in interpreting the required precision of assays to determine treatment cutoffs used in clinical outcomes trials,[12] and how this might translate to clinical decision-making if Lp(a)-lowering drugs are approved.

The primary determinant of differences in Lp(a) levels among various ancestries appears to be due to differences in *LPA* isoform size, except for nuances in individuals of African and possibly South Asian descent (as noted in subsequent text). The size of the major *LPA* isoform is moderately and inversely (R = approximately -0.55) associated with plasma Lp(a), primarily because small isoforms can be produced faster per unit time in the hepatocyte, thus leading to higher plasma Lp(a) levels. If the hypothesis is correct that humans emigrated out of Africa to the rest of the world, then one can speculate that each of these >40 *LPA* isoforms were randomly distributed worldwide and that founder effects also predominated. Although most of the *LPA* isoform data are derived from studies of European ancestry, sufficient data exist to support the notion that specific geographies, on average, accumulated different-sized isoforms.[13] The range of the major isoform size is similar across populations (1 to >40 kringle KIV_2 repeats), but the distribution of isoform size varies by ancestry and geography. Although variability exists, in general, individuals with European descent, represented in East and West Europe, Northern America, and Oceania, have a biphasic distribution, with the higher peak present on the smaller isoforms. Individuals from East Asia have a biphasic distribution, with the higher peak on the larger isoforms; individuals from South Asia tend to have equal distribution of large

ABBREVIATIONS AND ACRONYMS

apo(a) = apolipoprotein(a)

CVD = cardiovascular disease

ELISA = enzyme-linked immunoassay

K = kringle

LDL-C = low-density lipoprotein cholesterol

Lp(a) = lipoprotein(a)

SNP = single nucleotide polymorphism

FIGURE 1 Differences in Evolutionary Biology of Lp(a) in Different Species

Species	Kringles III	Kringles IV	Kringles V	Attachment to LDL	Protease Domain	Protease Activity	Fibrin Binding	OxPL (EO6) Binding
Plasminogen of all mammals Apolipoprotein(a)	✓	✓	✓	No	✓	✓	✓	✓
Human		✓	✓	✓	✓	No	✓	✓
Bonobo		✓	✓	✓	✓	No	No*	No
Chimpanzee		✓	✓	✓	✓	No	No*	No
Gorilla		✓	✓	✓	✓	No	No*	No
Orangutan		✓	✓	✓	✓	No	No	?
Baboon		✓		✓	✓	No	No†	No
Cynomolgous		✓		✓	✓	No	No*	No
Rhesus		✓		✓	✓	No	No*	No
Hedgehog	✓			✓	No	No	✓	No

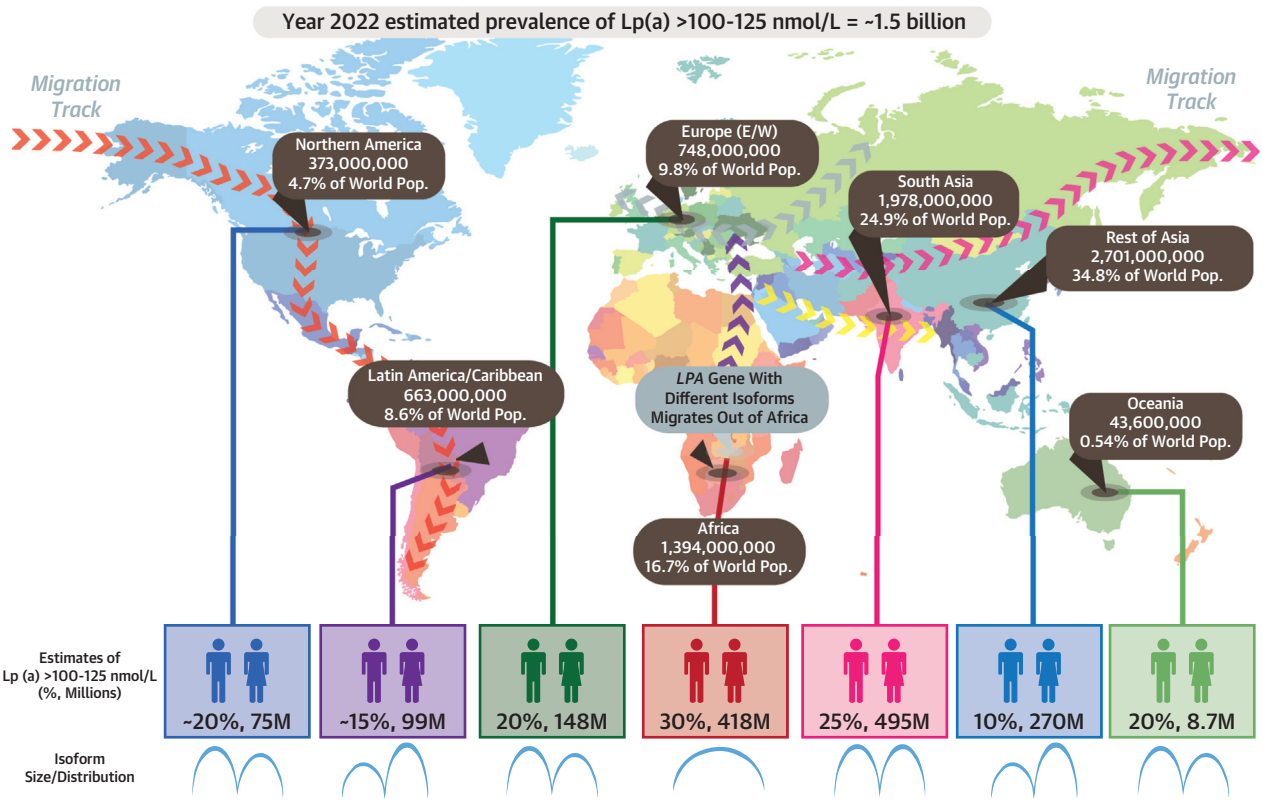
The figure depicts the presence of kringle III (KIII), KIV variants, KV, attachment of plasminogen or apolipoprotein(a) [apo(a)] to low-density lipoprotein (LDL) particles, the presence and functionality of a protease domain on plasminogen and apo(a), fibrin binding, and the presence of EO6 immunoreactivity signifying the presence of oxidized phospholipids (OxPL). The lysine binding site can influence both fibrin and OxPL binding *Contains the 7-amino acid lysine binding site, but does not bind fibrin due to amino acids substitutions (Asp57 to Asn57 in chimpanzee and gorilla, Trp72 to Arg72 in cynomogous and rhesus monkeys). †Contains an intact 7-amino acid lysine binding site, but absence of KV prevents fibrin binding. ? = data not available; E/W = East/West; Lp(a) = lipoprotein(a).

and small isoforms; and individuals from Africa exhibit a single peak (Figure 2). In the Dallas Heart Study of self-reported ancestry (1,831 Black, 1,047 White, and 603 Hispanic individuals), the distribution of the major apo(a) isoform reflects the global population means noted above (Figure 3A).[14] The shift to larger isoforms, and thus lower mean Lp(a) levels, is generally true for populations in East Asia, including Japanese[15] and Chinese[16] subjects but not South Asian subjects.[17,18] In the Dallas Heart Study, the median (IQR) Lp(a) levels, using the gold standard University of Washington Lp(a) enzyme-linked immunoassay (ELISA), were approximately 3-fold higher in Black individuals compared with White and Hispanic individuals (Figure 3B). However, the IQR was broad, and isoform size only explained 25% to 50% of plasma Lp(a) levels. Most studies of Lp(a) in different ancestral groups reflect this pattern.[19-23] For example, in UK Biobank, the largest and most contemporary study to date, compared with White individuals, population median Lp(a) levels were ~4-fold higher in individuals with African, 1.5-fold higher in individuals with South Asian, and 0.84-fold lower in individuals with Chinese ancestries. Additional genetic variants in the difficult-to-study repetitive KIV_2 region can be associated with lower or higher Lp(a) levels and may partially explain some of this variability.[24] Finally, in Black individuals, at every tertile of size of the major isoform, Lp(a) levels tended to be ~2 times higher (Figure 3C), for unknown reasons.

Although some studies have suggested that small isoforms independently contribute to additional risk, it has not been possible to disentangle this statistically from plasma Lp(a) levels, and in almost all studies when Lp(a) is added to multivariable analyses evaluating isoform size, their predictive value nearly or completely disappears.[24-26] Several single nucleotide polymorphisms (SNPs), in particular rs3798220 and rs10455972,[27] and genetic risk scores of multiple SNPs[28] have been associated with elevated Lp(a). However, these appear to be largely tagging SNPs of small isoforms and do not directly contribute to plasma levels. Importantly, not only does the prevalence of *LPA* SNPs vary significantly by ancestry, but one cannot predict plasma levels accurately, thus limiting their use in clinical care. For example, the C-allele of rs3798220 is present in ~3.5% of White individuals[27] and >40% of Hispanic individuals[25] but is absent in Black individuals living in Africa.[29] In White individuals, rs3798220 is associated with small isoforms and elevated Lp(a), but in U.S. Hispanic individuals, it is associated with large isoforms and low Lp(a) levels.

These data strongly support the notion that when evaluating Lp(a)-mediated CVD risk in subjects of different ancestries, the most predictive

FIGURE 2 **Global 2022 Prevalence of Elevated (≥100-125 nmol/L) Lp(a) Level**



The figure depicts the migration of the *LPA* gene. Due to different migration patterns of people with different-sized isoforms, as well as subsequent *LPA* gene remodeling, the worldwide prevalence of lipoprotein(a) (Lp[a]) plasma levels is variable. Prevalence of elevated Lp(a) (≥100-125 nmol/L) is based on year 2022 estimated world population prevalence data. Modified and updated with permission from Tsimikas et al.[4] M = million; Pop. = population.

measurement is the concentration of Lp(a) in plasma, as it summates all known and unknown variations in genetic, dietary, hormonal, and environmental risk factors that contribute to the plasma equilibrium.

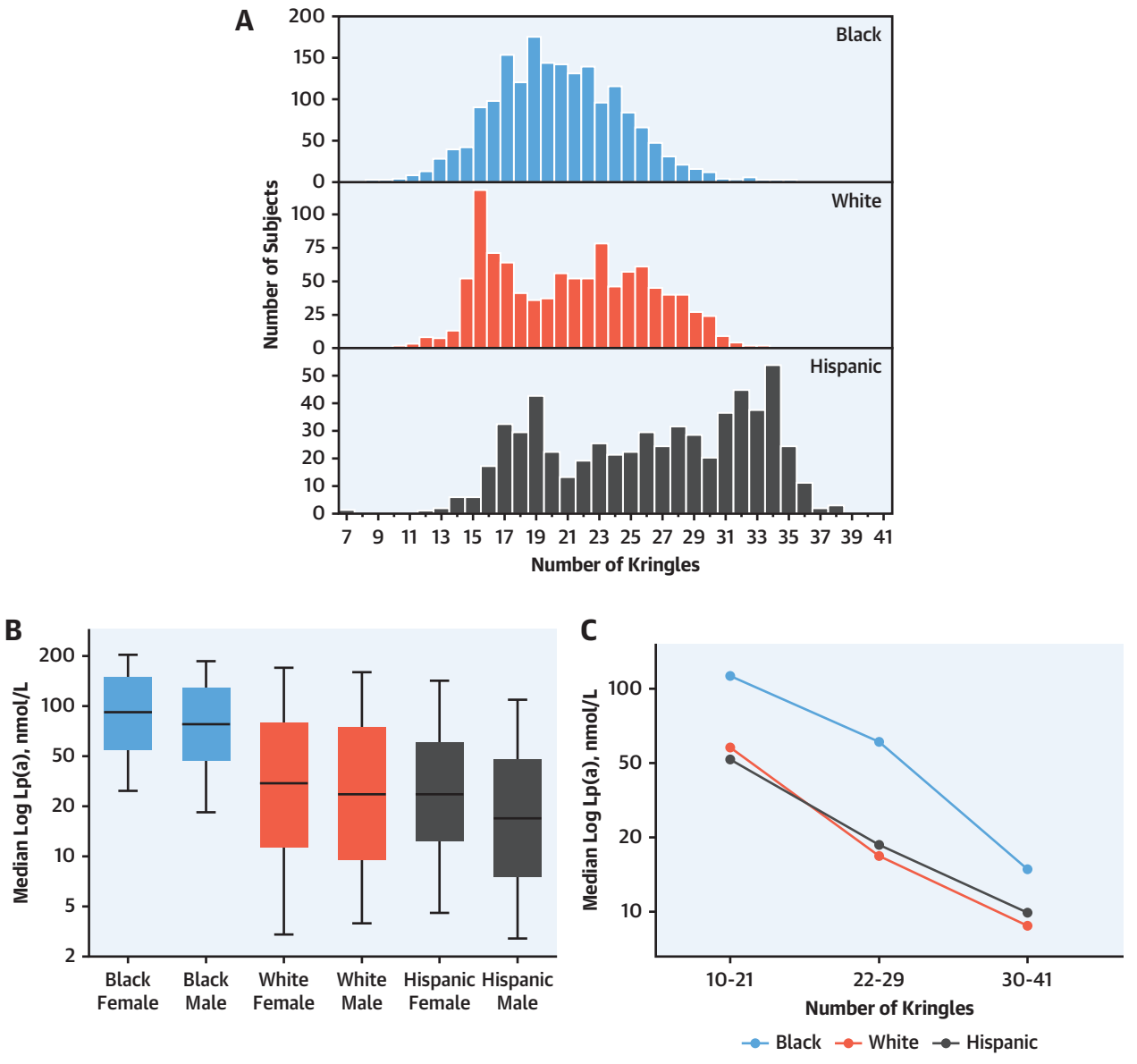
GUIDELINE RECOMMENDATIONS AND Lp(a) RISK THRESHOLDS

In the last 5 years, guidelines of at least 7 national and international societies have incorporated Lp(a) testing into their recommendations (**Table 1**). However, most did not provide ancestry-specific recommendations, except the American Association of Clinical Endocrinologists/American College of Endocrinology, which specifically recommend that Lp(a) be measured in individuals of South Asian or African descent. The European Atherosclerosis Society/European Society of Cardiology and Canadian Cardiovascular Society recommend all adults be tested for elevated Lp(a) at least once in their lifetime, and the other societies generally recommend screening intermediate or high-risk individuals, those with familial hypercholesterolemia, those with a family history of CVD, or those poorly responsive to other low-density lipoprotein cholesterol (LDL-C)-lowering therapies.

Lp(a) RISK THRESHOLDS AND ANCESTRY

For the purpose of this review, only studies that use measurements of Lp(a) are discussed, and not studies that report genetically elevated Lp(a) using kringle size or SNP data. In studies not necessarily reported by ancestry, elevated levels of Lp(a) are associated with higher CVD risk in primary and secondary prevention settings,[30,31] in subjects on statins with LDL-C levels <100 mg/dL,[32] and in the placebo groups of recent proprotein convertase subtilisin/kexin 9 inhibitor trials.[33,34] Elevated Lp(a) has been shown to be an independent risk factor in most clinical

FIGURE 3 Relationship of Predominant Isoform Size to Lp(a) Levels



(A) Frequency distribution of apolipoprotein(a) major isoform size in U.S. Black, White, and Hispanic individuals in the Dallas Heart Study. **(B)** Median log lipoprotein(a) (Lp[a]) in U.S. Black, White, and Hispanic female and male subjects. **(C)** Median log Lp(a) levels according to tertiles of the major isoform size.

subgroups studied, in particular the elderly[35] and patients with pre-existing diabetes.[36]

Several key large studies reporting comparative ancestry-specific outcomes data have been reported, including the ERFC (Emerging Risk Factors Collaboration) group,[30] ARIC (Atherosclerosis Risk In Communities),[23] MESA (Multi-Ethnic Study of Atherosclerosis),[22] Dallas Heart Study,[25] INTERHEART (The Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction),[21] UK Biobank,[20] and REGARDS (Reasons for Geographic and Racial Differences in Stroke)[19] (**Table 2**). Cardiovascular outcomes data in studies reporting ancestry and Lp(a) risk are heterogeneous almost by definition, and thus comparative analyses are challenging to perform. Cardiovascular outcomes have been reported as risk per 3.5 times higher than the usual Lp(a) or per 1 SD (in most studies, the range of Lp[a]

TABLE 1 Guideline and Consensus Statements on Measuring Elevated Lp(a)

	Lp(a) Risk Thresholds	Major Recommendation for Measuring Lp(a)
American Society of Apheresis, 2017[56]	>30 mg/dL (>45 nmol/L)	Subjects at intermediate or high risk, premature CVD, FH, family history of premature CVD without elevated LDL-C, or recurrent CVD despite statin treatment
ACC/AHA, 2018[57]	>50 mg/dL (>125 nmol/L)	Risk-enhancing factor at levels >50 mg/dL or >125 nmol/L. Family history of premature CVD or personal history of CVD not explained by major risk factors
ESC/EAS, 2019[58]	>50 mg/dL >180 mg/dL (>430 nmol/L) equivalent to heterozygous FH	At least once in each adult person's lifetime
NLA, 2019[46]	>50 mg/dL or >100 nmol/L (based on >80th percentile in Caucasian subjects)	Adults with personal history of premature CVD, or first-degree relatives with premature CVD, or LDL-C >190 mg/dL or suspected FH
HEART UK, 2019[42]	Risk thresholds: 32-90 nmol/L, minor 90-200 nmol/L, moderate 200-400 nmol/L, high >400 nmol/L, very high	Adults with a personal or family history of premature ASCVD; first-degree relatives who have Lp(a) levels >200 nmol/L patients with FH; patients with calcific aortic valve stenosis and those with borderline (but <15%) 10-year risk of a cardiovascular event
AACE/ACE, 2020[59]	>50 mg/dL	All patients with clinical ASCVD, premature or recurrent ASCVD despite LDL-C lowering; family history of premature ASCVD and/or increased Lp(a); South Asian or African ancestry, 10-year ASCVD risk ≥10% (primary prevention setting), personal or family history of aortic valve stenosis; patients with refractory elevations of LDL-C despite aggressive LDL-C–lowering therapy (ie, statin resistance)
Canadian Cardiovascular Society, 2021[60]	>50 mg/dL; >100 nmol/L in primary prevention	Once in a person's lifetime as a part of the initial lipid screening

AACE/ACE = American Association of Clinical Endocrinologists/American College of Endocrinology; ACC/AHA = American College of Cardiology/American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease (coronary heart disease plus ischemic stroke); ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FH = familial hypercholesterolemia; Lp(a) = lipoprotein(a); NLA = National Lipid Association.

per 1 SD is ~30-60 nmol/L), per Lp(a) 50 nmol/L increment, per HR/OR in quartiles or quintiles, as thresholds of ≥50 vs <50 nmol/L and ≥150 vs <150 nmol/L, and as race-specific percentiles/quartiles of Lp(a) levels.

Because the population mean of elevated Lp(a) varies, and because other risk factors may also be different among populations, the absolute risk of CVD can vary among ancestral groups and is generally higher as the population mean Lp(a) increases (**Table 2**). Although ancestral differences exist in Lp(a) levels, and differences are present in absolute risk, when the data are analyzed as proportional risk (eg, as per unit increase or threshold of Lp[a]), the relative increase among different ancestral groups in risk is roughly similar. This suggests that despite population mean differences, at the individual level, elevated Lp(a) levels seem to confer roughly similar risk (**Central Illustration**).

In the UK Biobank study, the absolute incidence rates of atherosclerotic CVD varied across racial groups, with an incidence per 1,000 patient-years of 5.92, 10.81, and 5.28 in UK White, UK South Asian, and UK Black individuals, respectively (**Figure 4A**). The overall slopes for the Lp(a) risk gradients, however, appeared similar for all 3 groups when analyzed as risk for person-years or by adjusted HRs (**Figures 4B to 4C**). In general, with some exceptions, the findings in the literature suggest that non-White individuals have proportional CVD risk with increasing Lp(a) similar to White individuals irrespective of which increment of Lp(a) change is used. The UK Biobank study included 460,506 middle-aged individuals, baseline mean LDL-C 137.5 mg/dL, and median Lp(a) 19.6 nmol/L, with >5.1 million person-years of follow-up time, and 22,401 incident CVD events, including 16,853 coronary artery disease events and 6,325 ischemic stroke events. Despite baseline differences in population mean Lp(a) levels and overall risk, the HRs for CVD per 50 nmol/L increase in Lp(a) were nearly identical, with HRs of 1.11, 1.10, and 1.07 for UK White, UK South Asian, and UK Black individuals (P for heterogeneity = 0.60). The HRs for CVD per Lp(a) ≥150 vs <150 nmol/L, present in 12.2% of those without and 20.3% of those with preexisting CVD, were 1.51, 1.37, and 1.13 for UK White, UK South Asian, and UK Black individuals but did not reach significance in UK Black individuals (P for heterogeneity = 0.15). Race-specific thresholds at ≥90th vs <90th percentile, which correspond to 168.2 nmol/L, 139.5 nmol/L, and 211.7 nmol/L in UK White, UK South Asian, and UK Black individuals, were all statistically significant with HRs of 1.52, 1.35, and 1.51.

Except for UK Biobank and the case-control study INTERHEART, the remaining studies included primarily subjects without prior CVD events, and the data cannot be extrapolated to individuals with prior CVD. In a subgroup analysis in the UK Biobank, among individuals with CVD at the time of

TABLE 2 Studies Reporting CVD Outcomes with Comparison Ancestry Data According to Plasma Lp(a) Levels

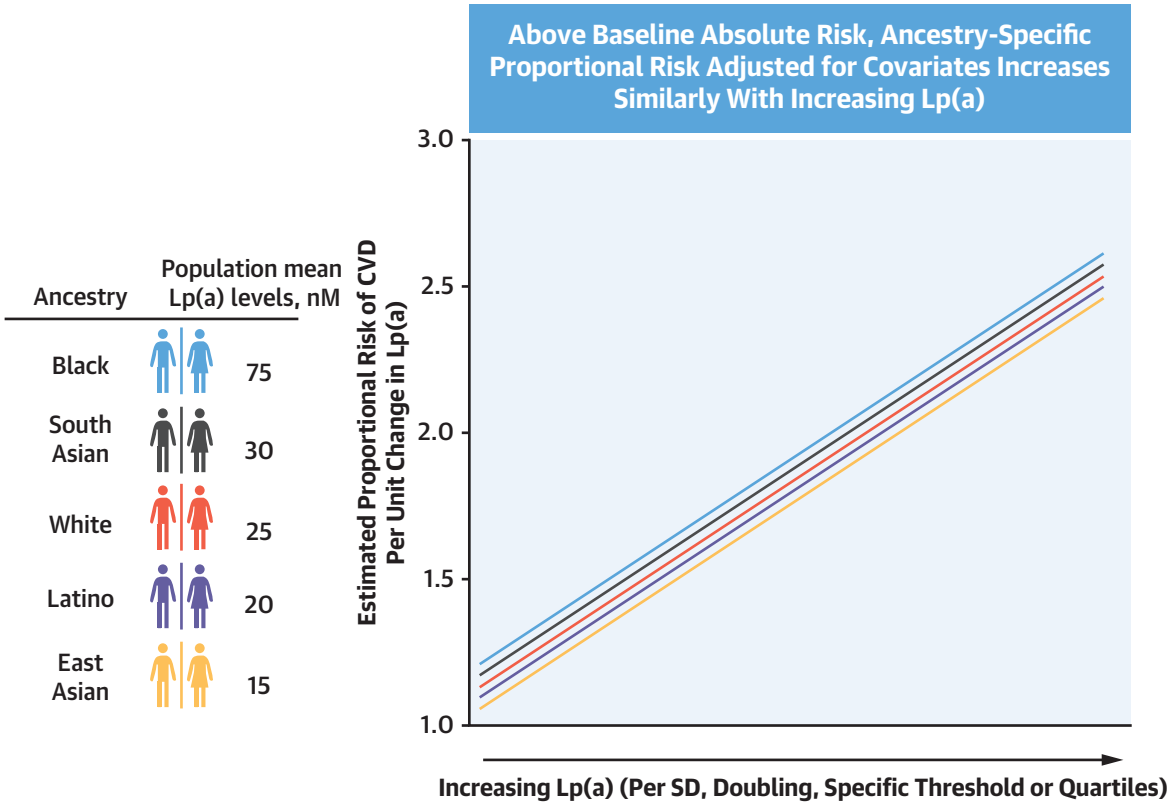
	Events/Subjects	Year	Follow-Up	Lp(a), Median (IQR)	OR/HR (95% CI)	
ERFC[30]		2009	1.3M pt y	**mg/dL**	**Per 3.5-X (~1 SD) usual Lp(a)**	
Black	261/4,546			12.6 (4.9-32.1)	CHD: 1.05 (0.90-1.23)	
White	7,540/95,753				CHD: 1.14 (1.09-1.19)	
ARIC[23]		2012	20 y	**mg/dL**	**Per 1 SD**	**HR Q5 vs Q1**
US Black	676/3,647			12.8 (7.1-21.7)	CVD: 1.13 (1.04-1.23) CHD: 1.11 (1.00-1.22) Stroke: 1.21 (1.06-1.39)	CVD: 1.35 (1.06-1.74)
White	1,821/9,851			4.3 (1.7-9.5)	CVD: 1.09 (1.04-1.15) CHD: 1.10 (1.05-1.16) Stroke: 1.07 (0.97-1.19)	CVD: 1.27 (1.10-1.47)
MESA[22]		2015	8.5 y	**mg/dL**	**CHD: Per 1 SD**	**Threshold ≥50 vs <50 nmol/L**
U.S. Black	66/1,323			35.1 (20.4-61.6)	1.49 (1.09-2.04)	1.69 (1.03-2.76)
U.S. White	102/1,677			12.9 (5.8-29.6)	1.22 (1.02-1.80)	1.82 (1.15-2.88)
U.S. Chinese	18/548			12.9 (7.7-23.4)	1.08 (0.65-1.80)	1.04 (0.22-4.98)
U.S. Hispanic	49/1,044			13.1 (6.3-28.8)	1.14 (0.86-1.50)	2.37 (1.17-4.78)
DHS[25]		2019	9.5 y	**nmol/L**		**MACE[a] HR Q4 vs Q1**
U.S. Black	146/1,792			79.0 (43-132)		3.01 (1.27-7.11)
U.S. White	52/1,030			26.9 (10-69)		1.83 (0.88-3.80)
U.S. Hispanic	13/597			21.3 (9-46)		5.43 (0.79-37.2)
INTERHEART[21]		2019	NA	**mg/dL (5%-95%)**		**MI OR Q4 vs Q1**
African	294/775			27.1 (4.1-110.6)		0.92 (0.65-1.31)
Arab	528/1,352			9.8 (2.3-53.4)		1.13 (0.80-1.59)
Chinese	234/443			18.1 (2.0-82.6)		1.62 (1.20-2.19)
European	951/856			11.5 (2.0-99.1)		1.36 (1.05-1.76)
Latin American	731/1,469			14.7 (2.0-100.0)		1.67 (1.25-2.22)
South Asian	948/1,829			18.9 (3.2-88.2)		2.14 (1.59-2.89)
SE Asian	507/1,221			12.9 (2.4-74.2)		1.83 (1.17-2.88)
UK Biobank[20]		2021	11.2 y	**nmol/L**	**ASCVD[b] Per Lp(a) 50 nmol/L**	**≥90th vs <90th Percentile**
U.K. White	18,764/41,7687			18.7 (7.4-72.7)	1.11 (1.10-1.12)	1.52 (1.46-1.59)
U.K. S. Asian	558/8,402			31.3 (11.9-69.4)	1.10 (1.04-1.16)	1.35 (1.03-1.78)
U.K. Black	242/7,013			74.8 (43.8-133.9)	1.07 (1.00-1.15)	1.51 (1.05-2.18)
REGARDS[19]		2022	~10 y	**nmol/L**	**CHD[c] per SD**	**CHD Q4 vs Q1**
Black	967/967			100.1 (47.5-185.8)	1.26 (1.02-1.56)	1.45 (0.78-2.69)
White	981/981			23.4 (8.2-112.9)	1.16 (1.02-1.31)	1.36 (0.93-1.98)
						CHD/Stroke Race-Specific Q4 vs Q1 1.68 (1.12-2.52) 1.34 (0.92-1.94)

DHS Quartiles (Q) for Lp(a): Q1 <19.6, Q2 >19.6 to <49.9, Q3 >49.9 to <110.5, and Q4 >110.5 nmol/L. Atherosclerosis Risk in Communities (ARIC): Q1-5 Black individuals, 0.1 to 6.1, >6.1 to 10.3, >10.3 to 15.8, >15.8 to 24, and >24 to 81.7. ARIC: Q1-5 White individuals, 0.1 to 1.5, >1.5 to 3.1, >3.1 to 6.0, >6.0 to 13.5, and >13.5 to 80.3. [a]Adjusted for sex, hypertension, diabetes mellitus, smoking, age in deciles, body mass index, low-density lipoprotein cholesterol per 25 mg/dL, high-density lipoprotein cholesterol per 10 mg/dL, and log2 triglyceride. [b]Composite of coronary artery disease (myocardial infarction and its acute complications, coronary artery bypass graft surgery, or percutaneous angioplasty/stent placement) and ischemic stroke (cerebral infarction due to thrombosis or cerebral atherosclerosis or cerebrovascular syndromes). [c]CHD events include a myocardial infarction hospitalization or CHD death (ie, a death suspected to be CHD related without evidence of a noncoronary cause).

CHD = coronary heart disease; CVD = cardiovascular disease (coronary heart disease plus ischemic stroke); DHS = Dallas Heart Study; ERFC = Emerging Risk Factors Collaboration; Lp(a) = lipoprotein(a); MACE = cardiac death, nonfatal myocardial infarction, stroke/transient ischemic attack, unstable angina requiring hospitalization, arterial revascularization; MESA = Multi-Ethnic Study of Atherosclerosis; MI = myocardial infarction; pt = patient; REGARDS = Reasons for Geographic and Racial Differences in Stroke.

enrollment, Lp(a) ≥150 nmol/L was associated with an adjusted HR of 1.16 (95% CI: 1.05-1.27) for a repeat atherosclerotic CVD event, with a statistically significant increase in risk for coronary artery disease (HR: 1.23; 95% CI: 1.10-1.37) but not for ischemic stroke (HR: 0.93; 95% CI: 0.77-1.12). However, the power was too low to present data by ancestry-specific analysis. Patients with prior CVD or multiple risk factors will be at significantly higher risk than the general population but will also be more

CENTRAL ILLUSTRATION **Population Mean Levels and Proportional Risk With Increasing Lp(a)**



Tsimikas S, et al. J Am Coll Cardiol. 2022;80(9):934–946.

Population mean lipoprotein(a) (Lp[a]) levels vary by ancestry, with highest to lowest in Black, South Asian, White, Latino, and East Asian individuals. The values roughly approximate published population mean levels. The incidence of cardiovascular disease (CVD) also differs among ancestries, due to differences in population mean Lp(a) levels, as well as differences in other risk factors for CVD. This is represented by various starting points for CVD risk. The multivariable-adjusted proportional risk of increasing Lp(a) is shown in the different colored lines, representing each of the ancestry categories. It is worth noting that the slope of the lines, despite different starting risk, is similar, suggesting that as CVD risk increases above the population mean, the Lp(a)-mediated risk is roughly similar in all ancestral groups shown. These estimated proportional risk relationships suggest that Lp(a) has an influence on CVD risk that is mostly independent of ancestry.

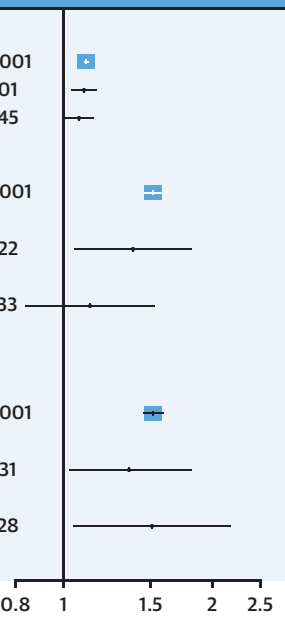
likely to be treated with aspirin and thienopyridines and LDL-C-lowering agents such as statins and proprotein convertase subtilisin/kexin 9 inhibitors. In a meta-analysis of statin-treated patients enrolled in 6 landmark trials of 29,069 subjects, it was shown that the associations of baseline and on-statin treatment Lp(a) with CVD risk were approximately linear, with increased risk of baseline Lp(a) ≥30 mg/dL overall or ≥50 mg/dL for patients receiving statins (a). Furthermore, the placebo groups of both FOURIER (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk)[33] and ODYSSEY OUTCOMES (Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab)[37] trials, with baseline LDL-C levels <100 mg/dL, showed continued Lp(a)-mediated risk despite statin therapy. Although ancestry-specific information was not provided in these studies, they do provide further evidence that Lp(a) is an independent risk factor of CVD in subjects with relatively well-controlled LDL-C.

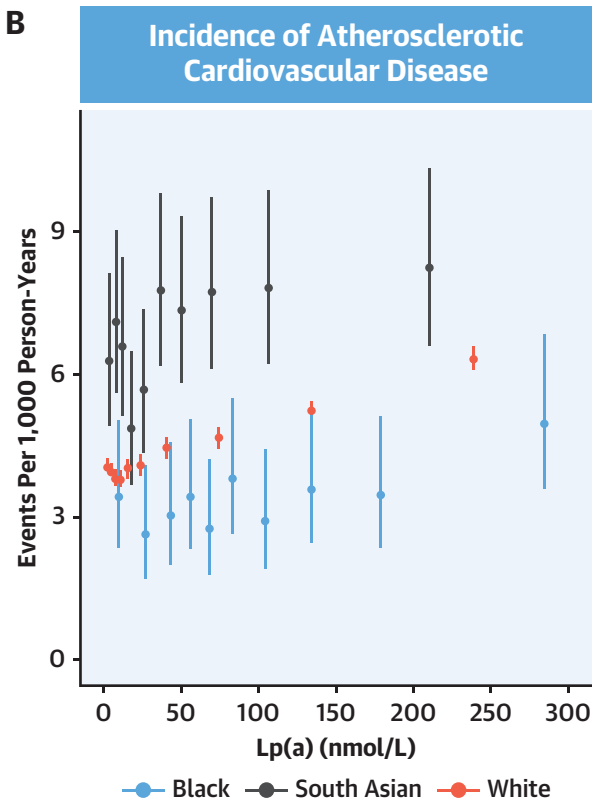
There are some limitations in the studies reporting on Lp(a) in different ancestry groups. Lp(a) risk data in general are primarily derived from White European populations. Additional studies are needed in diverse populations, which can be obtained at the trial design stage by a priori including appropriate proportions of patients with specific ancestries. Observational studies may include prespecified ancestral-specific analyses, such as ancestry-specific reclassification of risk to further define clinical relevance. Another

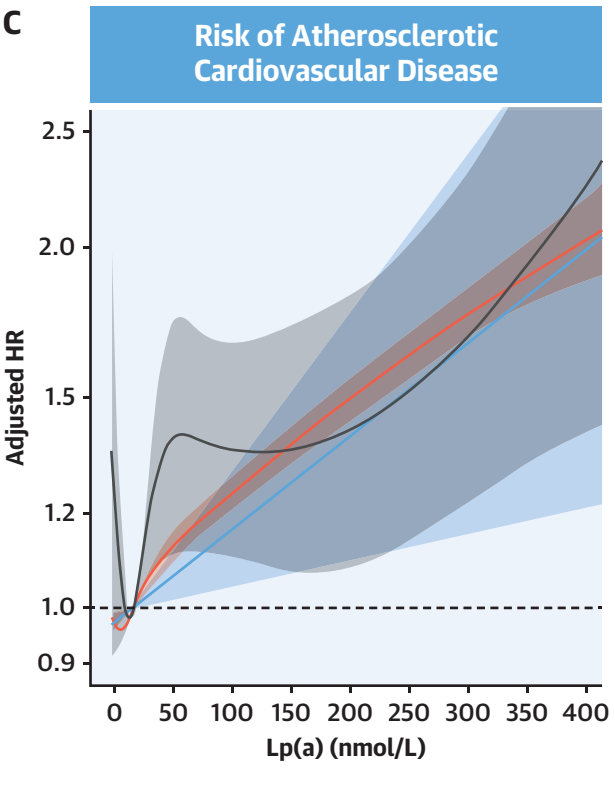
FIGURE 4 Incidence and Risk of Cardiovascular Disease According to Lp(a) Concentration

A

Race	Group	Affected/Total (%)	Incidence (Per 1,000 Person-Years)	HR	95% CI	*P* Value	*P* Heterogeneity
Per Lp(a) 50 nmol/L							
White		18,764/417,687 (4.5%)	5.92	1.11	(1.10-1.12)	< 0.0001	
South Asian		558/8,402 (6.6%)	10.81	1.10	(1.04-1.16)	0.001	0.60
Black		242/7,013 (3.5%)	5.28	1.07	(1.00-1.15)	0.045	
Threshold: Lp(a) = 150 nmol/L							
White	≥150 nmol/L	3,128/50,712 (6.2%)	8.11	1.51	(1.45-1.57)	< 0.0001	
	<150 nmol/L	15,636/366,975 (4.3%)	5.62				
South Asian	≥150 nmol/L	58/687 (8.4%)	14.40	1.37	(1.05-1.81)	0.022	0.15
	<150 nmol/L	500/7,715 (6.5%)	10.51				
Black	≥150 nmol/L	57/1,477 (3.9%)	6.01	1.13	(0.84-1.50)	0.433	
	<150 nmol/L	185/5,536 (3.3%)	5.09				
Threshold: Race-Specific 90th Percentile							
White	≥90th Percentile	2,537/40,580 (6.3%)	8.24	1.52	(1.46-1.59)	< 0.0001	
	<90th Percentile	16,227/377,107 (4.3%)	5.67				
South Asian	≥90th Percentile	58/663 (8.7%)	14.68	1.35	(1.03-1.78)	0.031	0.93
	<90th Percentile	415/6,179 (6.7%)	10.97				
Black	≥90th Percentile	34/695 (4.9%)	7.64	1.51	(1.05-2.18)	0.028	
	<90th Percentile	208/6,318 (3.3%)	5.03				







(A) HRs (95% CI) across different racial subgroups, analyzed by risk for every 50 nmol/L increase, concentrations ≥150 or <150 nmol/L, and race-specific 90th percentiles in lipoprotein(a) [Lp(a)] (White subjects, ≥168.2 nmol/L; South Asian subjects, ≥139.5 nmol/L; and Black subjects, ≥211.7 nmol/L). **(B)** Incidence rates per 1,000 person-years (95% CI) of atherosclerotic cardiovascular disease events grouped by decile of the Lp(a) distribution and stratified by racial subgroup. **(C)** Smoothed adjusted HRs (95% CI) of individuals with a given Lp(a) concentration with respect to the risk in an individual with the median population Lp(a) concentration (19.6 nmol/L) stratified by ancestry. The data are derived from UK Biobank and reprinted with permission from Patel et al.[20]

limitation is that race/ethnicity/ancestral constructs are self-identified and also rapidly changing in societies, which may partially explain some of the variability noted in population mean levels. Differences in *LPA* genetics may also exist within the accepted societal categories of ancestry. For example, it has been documented that differences exist in both isoform size and mean Lp(a) levels among different geographies in Africa,[38,39] which then further influence individual risk in those who migrated out of Africa to the rest of the world. Furthermore, individuals who self-identify as Hispanic have varied genetic backgrounds, and those with a larger percentage of African admixture, such as those from the Dominican Republic, tend to have higher Lp(a) levels (National Lipid Association 2022 abstract, Joshi PH, et al, oral presentation). The constantly changing admixture of population genetics adds additional limitations in developing ancestry-specific Lp(a) thresholds.

DIFFERENTIATION OF HIGH-RISK VS LOW-RISK SUBGROUPS

Early studies of risk of myocardial infarction in primary prevention settings suggested that Lp(a) ≥75 nmol/L was associated with inflection point of highest risk,[40] which was roughly confirmed by the ERFC[30] and the Lipoprotein Studies Collaboration meta-analyses.[32] The European Atherosclerosis Society has suggested Lp(a) approximately <100 to 125 nmol/L to be the optimal levels,[41] the threshold of which was based on the population mean of community-dwelling Northern Europeans and not necessarily the pathophysiological relationship to risk of Lp(a) that occurs at a lower level. The German guidelines for approval of apheresis require an Lp(a) level ≥60 mg/dL in the setting of controlled LDL-C and recurrent CVD events or progression of disease. Finally, the Lp(a) HORIZON (A Randomized Double-blind, Placebo-controlled, Multicenter Trial Assessing the Impact of Lipoprotein [a] Lowering With TQJ230 on Major Cardiovascular Events in Patients With Established Cardiovascular Disease) trial included Lp(a) approximately 2.5 times above normal as entry criteria into a secondary prevention outcomes trial. As the absolute and proportional risk of Lp(a) seems to be approximately linear above Lp(a) levels of 50 nmol/L, both in overall and in ancestry-adjusted analyses, one specific threshold to categorize individuals at high risk may be too simplistic. The HEART UK[42] 2019 consensus statement on Lp(a) proposed a graded risk threshold of CVD risk based on the following thresholds: minor risk, 32 to 90 nmol/L (~18-40 mg/dL), 67th to 80th population percentile; moderate risk, 90 to 200 nmol/L, 80th to 95th population percentile; high risk, 200 to 400 nmol/L, 95th to 99.8th population percentile; and very high risk, >400 nmol/L, >99.8th population percentile. In summary, minimal risk can be considered at <30-75 nmol/L, above which risk is roughly linear with increasing Lp(a) levels.

ARE CURRENTLY AVAILABLE CLINICAL ASSAYS ABLE TO DISCRIMINATE CVD RISK?

All commercially available assays use polyclonal antibodies specific to apo(a), which render the methods isoform dependent. However, among the different assays, one latex-enhanced turbidimetric method appears to be able to measure Lp(a) with a greatly reduced impact from the size polymorphism of apo(a).[43] This method is distributed by different manufacturers and optimized to be used on a variety of automated instruments. Although the binding of the polyclonal antibodies to latex particles may have the potential to somewhat minimize the size polymorphism of apo(a), the unique feature of this assay is the use of 5 independent sample pools selected to range from low to high Lp(a) levels. Consequently, the distribution of the apo(a) isoforms in each serum calibrator pool varies from predominantly large to predominantly small apo(a) isoforms, thus greatly minimizing the impact of the different apo(a) sizes in the samples.[4] A second isoform-independent method was recently reported[44] to be equivalent to the gold standard ELISA and to a novel liquid chromatography/tandem mass spectrometry[45] method.

As previously reported, evaluation of Lp(a) results obtained by the immunoturbidimetric method was performed on 80 fresh-frozen samples encompassing a large range of apo(a) isoforms and Lp(a) values from 8.7 to 276 nmol/L. Comparability of Lp(a) results was evaluated on 42 different analytical systems calibrated with the 5 independent standards after transfer of values from the World Health Organization/International Federation of Clinical Chemistry International reference material to the assay calibrators was performed and validated. The results of this comparison found an overall CV of 5.5% on the 80 analyzed samples, with a CV ranging from 10.5% in samples with low Lp(a) concentration to 2.1% in samples with high Lp(a).[4] The results were in excellent agreement with those obtained by using the gold standard monoclonal antibody ELISA, and only a modest bias related to apo(a) size variation was observed in all the evaluated systems. These results, obtained by different instruments and different lots

of calibrators, confirm that an excellent harmonization of Lp(a) results can be achieved if the values of the assay calibrators are rigorously verified. These data also confirm the suitability of Lp(a) values obtained by these assays to effectively discriminate CVD risk. Being traceable to the World Health Organization/International Federation of Clinical Chemistry reference material, these assays report Lp(a) values in nanomoles per liter in agreement with the scientific community proposal that Lp(a) levels be reported in molar concentration of apo(a).[4,46,47] However, to date, the U.S. Food and Drug Administration has only approved assays in milligrams per deciliter of total Lp(a) mass. Harmonization in Lp(a) reporting units is needed to achieve a correct interpretation of Lp(a) thresholds with clinical precision.

LABORATORY VS CLINICAL PRECISION OF Lp(a) ASSAYS

The precision of Lp(a) assays should be evaluated from 2 perspectives that have different goals and standards: the first from laboratory precision and the second from clinical precision. Laboratory precision is fundamental to the overall accuracy of the variable being measured and should be as precise as possible based on the chemical and biological allowances. However, at the clinical level, clinicians will be assessing risk more broadly and will be aiming to identify subjects at the highest risk that may affect treatment decisions. Furthermore, the natural variability in Lp(a) levels (approximately 25%) is higher than precision or variability (approximately <10%) in repeated measurement of the same sample in currently available laboratory-certified assays. Therefore, it will be difficult to assign a borderline value of a predefined threshold to assess error vs the day-to-day fluctuation of Lp(a) levels. These 2 variables will affect clinician judgment of how to identify the highest risk patients. Excessive emphasis on laboratory precision, vs clinical precision, can lead to mistrust of Lp(a) assays among clinicians so that they avoid measuring Lp(a) altogether and thus ignore Lp(a)-mediated risk.

Currently available Lp(a) assays are able to differentiate low- vs high-risk individuals with adequate precision at the bedside. In addition, there are intense efforts to develop globally standardized assays with new techniques, including targeted liquid chromatography/tandem mass spectrometry[45,48] and new isoform-independent monoclonal antibodies.[49] It is anticipated that by the time Lp(a)-lowering drugs are approved, Lp(a) assays will be globally standardized in molar units.

When a value is in the borderline range of a prespecified threshold with regard to clinical trial criteria (ie, approximately ≥150-175 nmol/L in Lp[a] HORIZON), the mean of 2 repeat measurements and clinical judgment can be used to determine appropriate clinical care. The number of patients falling within a close range of these values should be fairly small and have a negligible effect, particularly as this level is nearly 2.5 times above the continuum of the beginning of atherothrombotic risk.

CONFOUNDING VARIABLES IN Lp(a) PATHOPHYSIOLOGY THAT MAY AFFECT ACCURACY AND INTERPRETATION OF Lp(a) LEVELS IN ALL ANCESTRIES

Although the precision in laboratory methods, which should be <5% to 10%, may lead to modest variability in Lp(a) levels, natural, pathologic, or pharmacologic variability may occur that is larger in magnitude than laboratory precision and should be considered when interpreting Lp(a) values.

NATURAL VARIABILITY OF Lp(a) IN THE CONTEXT OF GENETICALLY DETERMINED BASELINE. More than 85% of plasma Lp(a) levels are genetically determined through the *LPA* gene. However, within this genetic context, Lp(a) values may vary ±25% on occasion, as noted by measuring serial blood samples in the placebo groups of randomized trials of Lp(a) lowering.[11] In comparison, there was generally less variability than noted with other lipid variables such as triglycerides, LDL-C, and apoB. The determinants of this variability may be partially due to diet and hormonal and inflammatory etiologies. For example, diets high in saturated fats, estrogen, testosterone, and hyperthyroidism may lower Lp(a), whereas hypothyroidism and inflammatory mediators such as interleukin-6 may raise Lp(a).[50]

ACUTE PHASE PROPERTIES OF Lp(a). The *LPA* gene contains several interleukin-6 response elements that can lead to higher production of apo(a) and Lp(a) assembly in states of acute or chronic inflammation. This may occur after acute myocardial infarction[51] or other severe illness such as COVID-19.[52] Interleukin-6 inhibitors have been shown to reduce Lp(a) levels approximately 30%.[53] The acute phase response of Lp(a) may be more prolonged than with other lipoproteins and may take 3 to 6 months to return to baseline.[54]

EFFECT OF CONCOMITANT MEDICATIONS. Most common drugs used to treat cardiovascular disease do not affect Lp(a) levels. However, evidence is accumulating, including a 5,280 patient-level meta-

analysis, that statins may increase Lp(a) levels 10% to 25%, with some subjects exhibiting extreme fluctuation.[55] The effect is usually noted within the first 1 to 3 months of statin initiation and should be considered in baseline risk evaluation. However, it is not known if any increase in Lp(a) post-statin therapy affects prognosis, and statins should not be discontinued if otherwise indicated.

CONCLUSIONS

Differences in population mean/median Lp(a) levels are present globally and vary by ancestry. Despite these differences, the proportional risk relative to baseline Lp(a) levels seems roughly similar among groups studied to date. Currently available Lp(a) assays are able to differentiate subjects with different ancestries at high risk from low risk. We propose that Lp(a)-mediated risk should be diagnosed and managed without applying modifications based on self-identified ancestry. These recommendations can be modified if new data emerge to support the use of specific risk thresholds for different ancestral groups.

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